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 IBM Technical Disclosure Bulletins

**Term:**

11 and 12 and 13

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<u>L4</u>	11 and 12 and 13	6	<u>L4</u>
<u>L3</u>	mg adj kg or g adj kg	73784	<u>L3</u>
<u>L2</u>	metastases	12836	<u>L2</u>
<u>L1</u>	wr-2721	99	<u>L1</u>

END OF SEARCH HISTORY

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- 
- ☐ 1. [20030086924](#). 10 Oct 02. 08 May 03. Treatment with anti-ErbB2 antibodies. Sliwkowski, Mark X.. 424/143.1; 424/155.1 A61K039/395.
- 
- ☐ 2. [20020132795](#). 03 May 02. 19 Sep 02. Methods for treatment of neuro- and nephro- disorders and therapeutic toxicities using aminothiols compounds. Stogniew, Martin, et al. 514/114; 514/625 514/646 514/665 A61K031/66 A61K031/135 A61K031/16 A61K031/13.
- 
- ☐ 3. [20020001587](#). 16 Mar 01. 03 Jan 02. Methods of treatment using anti-ErbB antibody-maytansinoid conjugates. Erickson, Sharon, et al. 424/178.1; A61K039/395.
- 
- ☐ 4. [6495129](#). 13 Oct 00; 17 Dec 02. Methods of inhibiting hematopoietic stem cells using human myeloid progenitor inhibitory factor-1 (MPIF-1) (Ckbeta-8/MIP-3). Li; Haodong, et al. 424/85.1; 514/12 514/2 514/8. A61K038/19.
- 
- ☐ 5. [6426366](#). 07 Apr 99; 30 Jul 02. Pharmaceutical compositions comprising tyrphostins. Novogrodsky; Abraham, et al. 514/523; 514/525. G61K031/275.
- 
- ☐ 6. [5994409](#). 09 Dec 97; 30 Nov 99. Methods for treatment of neuro--and nephro--disorders and therapeutic toxicities using aminothiols compounds. Stogniew; Martin, et al. 514/665; 514/114 514/649. A01N038/08 A01N057/00 A01N033/02.
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Terms	Documents
11 and 12 and 13	6

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=> d his

(FILE 'HOME' ENTERED AT 17:10:46 ON 15 MAY 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 17:11:01 ON 15 MAY 2003

L1 2610 S WR-2721  
L2 27 S METASTASES AND L1  
L3 0 S MG/KG OR G/KG  
L4 840460 S MG(W)KG OR G(W)KG  
L5 9 S L2 AND L4  
L6 5 DUP REM L5 (4 DUPLICATES REMOVED)

=> d bib ab 1-5 16

L6 ANSWER 1 OF 5 SCISEARCH COPYRIGHT 2003 THOMSON ISI  
AN 2002:19970 SCISEARCH  
GA The Genuine Article (R) Number: 504WB  
TI Inhibition of spontaneous **metastases** formation by amifostine  
AU Grdina D J (Reprint); Kataoka Y; Murley J S; Hunter N; Weichselbaum R R;  
Milas L  
CS Univ Chicago, Dept Radiat & Cellular Oncol, MC1105, Rm E-SB-11B, 5841 S  
Maryland Ave, Chicago, IL 60637 USA (Reprint); Univ Chicago, Dept Radiat &  
Cellular Oncol, Chicago, IL 60637 USA; Univ Texas, MD Anderson Canc Ctr,  
Dept Expt Radiat Oncol, Houston, TX 77030 USA  
CYA USA  
SO INTERNATIONAL JOURNAL OF CANCER, (10 JAN 2002) Vol. 97, No. 2, pp.  
135-141.  
Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK,  
NY 10158-0012 USA.  
ISSN: 0020-7136.  
DT Article; Journal  
LA English  
REC Reference Count: 36  
\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*  
AB Amifostine was investigated for its ability to inhibit spontaneous  
**metastases** formation using the well-characterized murine sarcoma,  
Sa-NH. Amifostine was administered intraperitoneally at a dose of 50  
**mg/kg** every other day for 6 days to C3Hf/Kam mice until  
tumors reached an average size of 8-8.5 mm in diameter. Amifostine was  
again administered immediately after surgical removal of the tumor-bearing  
limbs by amputation, and then once more 2 days later. Twenty-one days  
later, animals were evaluated for the presence of spontaneously developed  
pulmonary **metastases**. Nontumor-bearing control animals were sham  
treated using the same dosing and surgery schedules. Treatment with  
amifostine appeared to slightly delay tumor growth, that is, 13 vs. 12  
days for tumors to reach an average diameter of 8 mm. Amifostine reduced  
both the incidence of pulmonary **metastases** formed in  
experimental animals from 77% to 57% ( $p < 0.05$ ), and their average number  
per animal from  $12.8 \pm 5.4$  (SEM) to  $2.9 \pm 1.1$  (SEM). The effect  
of amifostine exposure on serum levels of the angiogenesis inhibitor  
angiostatin was also determined using Western blot analysis. Consistent  
with the antimetastatic effect, exposure of animals to 50 **mg/**  
**kg** of amifostine resulted in a 4-fold enhanced serum level of  
angiostatin above control levels. This phenomenon occurred in  
tumor-bearing and nontumor-bearing animals. The effects of amifostine on  
matrix metalloproteinase (MMP) enzymatic activity was also determined  
using gelatin zymography. Conditioned growth medium collected from Sa-NH  
cells grown to confluency was exposed to various concentrations of SH,  
i.e., 2-[(aminopropyl)amino]ethane-thiol (WR-1065), the active thiol form  
of amifostine, for either 30 min or 18 hr. WR-1065, as a function of  
increasing dose and time, inhibited the enzymatic activities of MMP-2 and  
MMP-9. At a concentration and time of exposure likely to be achieved in

vivo, that is, 40  $\mu$ M and 30 min, MMP-2 and MMP-9 activities were reduced to between 30% and 40% of control values. Consistent with these affects, WR-1065 was also found to be effective in inhibiting the ability of Sa-NH cells to migrate through Matrigel membranes. After an 18-hr exposure under in vitro conditions, WR-1065 at concentrations of 4, 40 and 400  $\mu$ M, and 4 mM, inhibited Sa-NH migration to 11%, 44%, 81% and 97% of control values, respectively. The abilities of amifostine and its active thiol WR-1065 to stimulate angiostatin production in mice, and to inhibit the MMP enzymatic activities and invasion ability of Sa-NH cells under in vitro conditions, are consistent with the observed antimetastatic effects exhibited against Sa-NH tumors growing in vivo. (C) 2002 Wiley-Liss, Inc.

L6 ANSWER 2 OF 5 MEDLINE DUPLICATE 1  
 AN 88114786 MEDLINE  
 DN 88114786 PubMed ID: 2828290  
 TI Influence of misonidazole, SR-2508, RSU-1069 and **WR-2721**  
 on spontaneous **metastases** in C57BL mice.  
 AU Kanclerz A; Chapman J D  
 CS Department of Radiation Oncology, Cross Cancer Institute, University of  
 Alberta, Edmonton, Canada.  
 SO INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS, (1988 Feb)  
 14 (2) 309-16.  
 Journal code: 7603616. ISSN: 0360-3016.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 198803  
 ED Entered STN: 19900308  
 Last Updated on STN: 19900308  
 Entered Medline: 19880310  
 AB The effect of treatments with the hypoxic cell radiosensitizers  
 misonidazole (MISO), SR-2508, RSU-1069, and with the radioprotector  
**WR-2721** on spontaneously disseminated Lewis lung  
 carcinoma (LLC) and B16 melanoma (B16M) was investigated. Tumors were  
 implanted into the tails of C57BL mice and were surgically removed after  
 reaching volumes of approximately 40 mm<sup>3</sup>. This technique results in the  
 induction of metastatic disease in lungs and at other anatomical sites and  
 allows the independent treatment of disseminated tumor cells. The  
 radiosensitizers and the radioprotector were administered 24 hr after  
 surgery and animals were killed 14 and 30 days after removal of LLC and  
 B16M, respectively. The time to death from spontaneous **metastases**  
 was also measured. Both single treatments with large doses of MISO (1.0  
**g/kg**) and fractionated therapy with smaller doses (0.5  
**g/kg** on 5 consecutive days) promoted the formation of  
**metastases** to the lungs, lymph nodes and other organs. The  
 survival times of MISO treated animals did not differ from control animals  
 but manifestation of metastatic disease in the lungs and other organs  
 occurred at earlier times. Administration of equitoxic doses of SR-2508  
 (3.0 **g/kg**) and RSU-1069 (0.1 **g/kg**)  
 also promoted **metastases** formation. Mice treated with these  
 radiosensitizers developed more **metastases** in the lungs and at  
 other sites. Treatment with a single dose of **WR-2721**  
 (0.4 **g/kg**) promoted lung **metastases** but  
 exerted a suppressive effect on lymph node tumors. When the  
 radioprotector was given in fractionated schedules in three different  
 doses (0.05 **g/kg**, 0.1 **g/kg** and 0.2  
**g/kg** for 10 consecutive days) a slight enhancement of  
 lung **metastases** and suppression of extrapulmonary  
**metastases** was observed.

L6 ANSWER 3 OF 5 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
 AN 1984:324712 BIOSIS  
 DN BA78:61192

TI PROTECTION BY S-2-3 AMINOPROPYLAMINOETHYLPHOSPHOROTHIOIC-ACID AGAINST  
 RADIATION INDUCED AND CYCLO PHOSPHAMIDE INDUCED ATTENUATION IN ANTI TUMOR  
 RESISTANCE.  
 AU MILAS L; MCBRIDE W H; HUNTER N; ITO H  
 CS DEP. EXPERIMENTAL RADIOTHERAPY, UNIV. TEX. M. D. ANDERSON HOSPITAL TUMOR  
 INST., HOUSTON, TX 77030.  
 SO CANCER RES, (1984) 44 (6), 2382-2386.  
 CODEN: CNREA8. ISSN: 0008-5472.  
 FS BA; OLD  
 LA English  
 AB Studies were performed to investigate whether S-2-(3-  
 aminopropylamino)ethylphosphorothioic acid (WR-2721)  
 can protect antitumor immune rejection responses against the damaging  
 effects of whole-body irradiation (WBI) and cyclophosphamide (CY). Among  
 these damaging effects were radiation-induced enhancement of s.c. tumor  
 take and radiation- and CY-induced enhancement of lung colonization by  
 tumor cells injected i.v. The ability of WR-2721 to  
 protect against WBI-induced decreased radio response of solitary tumors  
 was also investigated. All experiments were performed with an immunogenic  
 fibrosarcoma syngeneic to C3Hf/Kam mice. WR-2721 was  
 given i.p. at a dose of 400 mg/kg 30 min before WBI  
 with .gamma.-rays or CY injection. WBI with 650 rads reduced the number of  
 tumor cells needed for tumor take in 50% of animals from 5.1 .times. 10<sup>4</sup>  
 cells in normal mice to 2.0 .times. 10<sup>2</sup>. WR-2721 given  
 before WBI almost entirely abolished the effect of WBI: the number of  
 tumor cells needed for tumor take in 50% of animals was 1.4 .times. 10<sup>4</sup>.  
 Treatment of mice with WBI or CY increased the number of tumor nodules in  
 the lung generated by fibrosarcoma cells injected i.v. 5 days later, in a  
 linear dose response. WR-2721 greatly reduced this  
 metastasis enhancement effect of WBI and CY with protection factors of 2.5  
 for WBI and 1.8 for CY. Fibrosarcomas of 8 mm in diameter exhibited a  
 decreased radiocurability when growing in WBI mice: the dose of  
 irradiation yielding local tumor control in 50% of animals in these mice  
 was 5950 compared to a dose of irradiation yielding local tumor control in  
 50% of animals of 4160 rads in normal mice. WR-2721  
 given before WBI inhibited this effect of WBI: the dose of irradiation  
 yielding local tumor control in 50% of animals was 5210 rads. The  
 proportion of macrophages in tumors growing in WBI mice was significantly  
 reduced, but not when WR-2721 was first given.  
 WR-2721 greatly reduced the damaging effects of WBI and  
 CY on natural killer cell activity. Therefore, WR-2721  
 was capable of protecting the immune mechanisms involved in antitumor  
 resistance against WBI and CY. This might be of therapeutic benefit when  
 WR-2721 is combined with radio- or chemotherapy.

L6 ANSWER 4 OF 5 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
 AN 1984:292580 BIOSIS  
 DN BA78:29060  
 TI EFFECT OF TUMOR TYPE SIZE AND END POINT ON TUMOR RADIOPROTECTION BY  
 WR-2721 S-2-3 AMINOPROPYLAMINO ETHYL  
 PHOSPHOROTHIOIC-ACID.  
 AU MILAS L; HUNTER N; ITO H; PETERS L J  
 CS DEPARTMENT OF EXPERIMENTAL RADIOTHERAPY, M.D. ANDERSON HOSPITAL, 6723  
 BERTNER AVE., HOUSTON, TEXAS 77030.  
 SO INT J RADIAT ONCOL BIOL PHYS, (1984) 10 (1), 41-48.  
 CODEN: IOBPD3. ISSN: 0360-3016.  
 FS BA; OLD  
 LA English  
 AB Experiments are reported showing that the degree of tumor radioprotection  
 afforded by WR-2721 (S-2-(3-aminopropylamino)-  
 ethylphosphorothioic acid) varies with the type of tumor and assay  
 endpoint, and that for a given tumor system, microaggregates are protected  
 better than larger cell masses. The tumor used were a  
 methylcholanthrene[carcinogen]-induced fibrosarcoma [murine] (FSa), and 2

tumors of spontaneous origin, another fibrosarcoma (NFSa), and a mammary carcinoma (MCa-4), all syngeneic to C3Hf/Kam mice. **WR-2721** was given in a dose of 400 **mg/kg** 30 min before irradiation in all experiments. In TCD50 assays, **WR-2721** protected 5 mm diameter and impalpable 3 day old transplant of 5 .times. 105 FSA cells growing in the leg by factors of 1.11 and 1.13, respectively. Using the tumor latency endpoint, 3 day-old s.c. transplants of 103 FSA in the abdominal wall were protected by a factor of 1.27, a degree of protection similar to that reported earlier for sterilization of lung micrometastases of the same tumor. MCa-4 tumors growing in the leg were protected better than FSA in TCD50 assays with protection factors of 1.3 for 4 day old transplants, 1.24 for 5 mm tumors, and 1.23 for 8 mm tumors. MCa-4 tumors recurrent after irradiation as 4 day old transplants grew more rapidly in mice that received **WR-2721**, and this was shown to be most likely due to protection by the drug against expression of the tumor bed effect. Using the lung micrometastases assay, NFSa was protected by a factor of 1.22. This variability in protection with different tumor types, sizes and assay endpoints is discussed in terms of drug delivery and uptake, and also in relation to the influence of tumor hypoxia on the radioprotective ability of **WR-2721**.

L6 ANSWER 5 OF 5 MEDLINE DUPLICATE 2  
 AN 83206571 MEDLINE  
 DN 83206571 PubMed ID: 6303574  
 TI Effect of tumor size on S-2-(3-aminopropylamino)ethylphosphorothioic acid and misonidazole alteration of tumor response to cyclophosphamide.  
 AU Milas L; Ito H; Hunter N  
 NC CA-06294 (NCI)  
 SO CANCER RESEARCH, (1983 Jul) 43 (7) 3050-6.  
 Journal code: 2984705R. ISSN: 0008-5472.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 198307  
 ED Entered STN: 19900319  
 Last Updated on STN: 19970203  
 Entered Medline: 19830729  
 AB The influence of tumor size on the ability of S-2-(3-aminopropylamino)ethylphosphorothioic acid (**WR-2721**) or misonidazole (MISO) to alter cyclophosphamide (CY) antitumor activity was investigated, using a chemically induced fibrosarcoma (FSA) and a spontaneous fibrosarcoma (NFSa) in C3Hf/Kam mice. Tumors were of two sizes at the time of treatment, 8-mm leg tumors and 4-day-old micrometastases in the lung. The antitumor activity of CY and its modification were assessed by growth delay of leg tumors and the reduction in the number of lung **metastases**. Both measures of tumor response were more pronounced as the dose of CY increased, and FSA was more sensitive to CY than was NFSa. **WR-2721** (400 **mg/kg**), given 30 min before treatment with CY, reduced the effectiveness of CY on both FSA and NFSa. This reduction in effectiveness of CY was only minimal for leg tumors (dose-modifying factors were 1.1 for FSA and 1.03 for NFSa) but remarkable for lung micrometastases (dose-modifying factors were 1.81 for FSA and 1.55 for NFSa). Protection increased with the increase in the dose of **WR-2721** and was also dependent on the time of injection relative to CY. The greatest protection occurred when **WR-2721** was given within 30 min before to 15 min after CY. Tumor size had the opposite effect on MISO from that on **WR-2721**. MISO (1 **mg/g**) enhanced the effect of CY more effectively for leg tumors than for lung micrometastases: dose-modifying factors were 1.74 for FSA and 2.21 for NFSa growing in the leg and 1.27 for FSA and 1.11 for NFSa lung micrometastases. Therefore, tumor size appears to be a very important

factor in determining the extent of **WR-2721**- and  
MISO-induced modification of CY antitumor effect.

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(FILE 'HOME' ENTERED AT 11:30:51 ON 15 MAY 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 11:31:01 ON 15 MAY 2003

L1 3344 S WR(W) (2721 OR 1065 OR 638 OR 77913 OR 33278 OR 3689 OR 2822 O  
L2 29241 S (DIFFICULT? OR PROBLEM OR PITFALL OR DRAWBACK) (8A) (CANCER OR  
L3 6 S L1 AND L2  
L4 3 DUP REM L3 (3 DUPLICATES REMOVED)

=> d bib ab 1-3 14

L4 ANSWER 1 OF 3 MEDLINE DUPLICATE 1  
AN 2001294068 MEDLINE  
DN 21271445 PubMed ID: 11379297  
TI Amifostine (Ethyol) as modulator of hepatic and biliary toxicity from  
intraarterial hepatic chemoembolization: results of a phase I study.  
AU Fiorentini G; Giovanis P; Leoni M; De Giorgi U; Cariello A; Dazzi C;  
Caldeo A  
CS Oncology Department, City Hospital, v.le Randi 5, Ravenna 48100, Italy..  
oncologia@ra.nettuno.it  
SO HEPATO-GASTROENTEROLOGY, (2001 Mar-Apr) 48 (38) 313-6.  
Journal code: 8007849. ISSN: 0172-6390.  
CY Greece  
DT (CLINICAL TRIAL)  
(CLINICAL TRIAL, PHASE I)  
Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 200110  
ED Entered STN: 20011015  
Last Updated on STN: 20011015  
Entered Medline: 20011011  
AB BACKGROUND/AIMS: Hepatic and biliary toxicity are still significant  
**problems** after intraarterial hepatic chemoembolization for liver  
**metastases** from large bowel cancers. In about 30-60% of the  
patients hepatic and biliary toxicity are the limiting aspects of  
intraarterial hepatic chemoembolization and exclude a lot of patients from  
a repeated beneficial treatment. Amifostine (Ethyol) is a prodrug that  
must be dephosphorylated to the free thiol in which form it can detoxify  
free oxygen radicals generated by radiation, hypoxia and by drugs such  
anthracyclines, platinum analogues and alkylating agents. Amifostine as  
inactive prodrug is primarily metabolized at the tissue site by membrane  
alkaline phosphatase, which is highly active in the cell membranes of  
normal endothelial cells and biliary tree cells but not in the cell  
membranes and neovascular capillaries of tumor. When dephosphorylated to  
**WR-1065**, amifostine is rapidly taken up into normal  
liver cells by a carrier-mediated facilitated diffusion transport process.  
The resulting high thiol content in normal liver tissue (biliary cells and  
hepatocytes) compared with the negligible concentration in liver  
metastases from large bowel cancers probably provides for selective drug  
resistance to intraarterial hepatic chemoembolization protecting normal  
tissue and allowing full therapeutic effect on tumor. **METHODOLOGY:** From  
May 1997 we planned a phase I study in patients receiving intraarterial  
hepatic chemoembolization for liver metastases from large bowel cancers.  
We started at 200 mg/m<sup>2</sup> dissolved in 250 cc of normal saline given in 15  
min in the intrahepatic artery 20 min before an intraarterial hepatic  
chemoembolization consisting of mitomycin 10 mg/m<sup>2</sup>, epirubicin-50,  
cisplatin-60 diluted in 10 mL of contrast media, mixed in 15 mL of  
lipiodol UF followed by a gelfoam powder solution until stagnation of the  
flow. The escalating dose, every 3 patients, was: 200 mg/m<sup>2</sup>, 250 mg/m<sup>2</sup>,  
300 mg/m<sup>2</sup>, 350 mg/m<sup>2</sup>. **RESULTS:** Toxicity has been observed at 350 mg/m<sup>2</sup>: 1  
patient reported transient hypotension (Blood pressure 70/50 mm Hg), 1



patient had skin flushing and dyspnoea. 300 mg/m<sup>2</sup> are well tolerated and seem to reduce the level of transaminases, lactic acid dehydrogenase, and gamma-glutamyl transferase. Also the duration of necrotic damage, always observed after intraarterial hepatic chemoembolization, seems shorter compared with historical controls. CONCLUSIONS: Amifostine can be certainly administered at 300 mg/m<sup>2</sup> as intraarterial infusion and could be a significant step to ameliorate the therapeutic ratio of intraarterial hepatic chemoembolization.

L4 ANSWER 2 OF 3 SCISEARCH COPYRIGHT 2003 THOMSON ISI

AN 93:210382 SCISEARCH

GA The Genuine Article (R) Number: KU669

TI COLORECTAL-CANCER - WHATS NEW IN 1992

AU RIVOIRE M (Reprint)

CS CTR LEON BERARD, DEPT CHIRURG, 28 RUE LAENNEC, F-69373 LYON, FRANCE (Reprint)

CYA FRANCE

SO PATHOLOGIE BIOLOGIE, (DEC 1992) Vol. 40, No. 9BIS, pp. 943-948. ISSN: 0369-8114.

DT Article; Journal

FS LIFE

LA French

REC Reference Count: 3

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Five studies presented at the 1992 ASCO meeting are analysed. Kligerman's study was designed to determine if pre-treatment with **WR-2721** could protect normal tissues from the toxicities induced by radiation therapy (in 100 patients with advanced rectal cancer). This pre-treatment resulted in a 13 % reduction of moderate and severe acute toxicity. No **WR-2721** patient experienced moderate or severe late toxicities compared to five in the group without pre-treatment. The complete response rate was higher in the **WR-2721** group and there was no major **WR-2721** related toxicity. Minski studied the acute toxicity (during treatment and two weeks after) of combined pelvic radiation therapy, 5-FU and leucovorin when delivered pre-operatively (16 patients) versus post-operatively (25 patients) in patients with rectal cancer. The toxicity criteria were fatigue, diarrhea, tenesmus, bowel movements, dysuria and erythema. Grade 3+ toxicity was more important in the post-operative therapy group (48 % versus 13 %). Given this high incidence of grade 3+ toxicity future randomized trials should explore the pre-operative approach. The final report of the inter group study of 5-FU plus levamisole as adjuvant therapy for stage C colon cancer was made by Moertel. With a median follow-up time of 5.5 years, the 5-FU plus levamisole treatment has reduced the recurrence rate by 39 %, the cancer related death rate by 32 % and the overall death rate by 31 %. Most of the recurrences occurred during the first two years. There was a decrease in the liver, great omentum, peritoneum and lung metastases, but there was no modification in loco-regional recurrence rate. Welt presented a phase I/II study of radio-immunotherapy with I-131-monoclonal antibody A33 in patients with advanced colorectal carcinoma. Results were characterised by major hematologic toxicity and minor tumor response rate. This study (from a leading research team working with one of the best monoclonal antibody) outline the extreme **difficulty** of **cancer** therapy with radio-labeled monoclonal antibody. Humanization of A33 is planned to improve these results. Heiss undertook a prospective study to evaluate the influence of homologous blood transfusion on recurrence rate after colorectal cancer surgery. Fifty-eight patients receiving autologous blood transfusion were compared with sixty-two patients receiving homologous transfusion. With a median follow-up of 21 months a higher recurrence rate was found in the homologous group (29.4 % versus 16.7 %). This study methodology is rather criticizable, but its main interest is to focus on the immunosuppressive effect of blood transfusion during surgery in cancer patients.

L4 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS  
AN 1987:644616 CAPLUS  
DN 107:244616  
TI Chemical radioprotectors: assessment and prospects  
AU Fatome, M.  
CS Div. Radiobiol. Radioprot., Cent. Rech. Serv. de Sante des Armees,  
Clamart, 92141, Fr.  
SO Radioprotection (1987), 22(3), 209-18  
CODEN: RAPRBA; ISSN: 0033-8451  
DT Journal; General Review  
LA French  
AB The best radioprotective compds. are still aminothiols, the most  
active being the phosphorothioate WR 2721. In spite  
of clin. trials carried out in the United States with this compd. because  
of its low or negligible effect on **tumor** cells, their human  
application presents some **difficulties**, the most important  
coming from the risk of appearance of side-effects. An enhancing of their  
activity and a lowering of their toxicity have been obtained with new  
assocns. of compds. and, concerning the oral way, by their incorporation  
into carriers. Their action mechanisms is complex and multiple. Except  
free radical scavenging, hypoxia and glutathion peroxydase activation are  
certainly important factors. They have no action on the incidence of  
radio-induced nausea and vomiting, the prevention of which remains  
difficult. On the other hand, at least some of them seem to have an  
antimutagenic and antineoplastic effect, even if given after irradiation. 35  
Refs.

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(FILE 'HOME' ENTERED AT 13:32:15 ON 15 MAY 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 13:32:34 ON 15 MAY 2003

L1 2610 S WR-2721  
L2 29218 S LUNG(6A)METASTAS?  
L3 21 S L1 AND L2  
L4 12 DUP REM L3 (9 DUPLICATES REMOVED)  
L5 1818 S (REDUC? OR DIMINISH? OR DECREAS? OR INHIBIT?) (7A)LUNG(6A)META  
L6 3934 S (REDUC? OR DIMINISH? OR DECREAS? OR INHIBIT?) (7A)LUNG(6A)META  
L7 6 S L1 AND L6  
L8 4 DUP REM L7 (2 DUPLICATES REMOVED)

=> d bib ab 1-4 l8

L8 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2003 ACS  
AN 2000:688056 CAPLUS  
DN 133:247270  
TI Phosphorothioates and phosphorothioate metabolites for protection against  
tumor metastasis formation  
IN Grdina, David J.; Milas, Luka  
PA Arch Development Corp., USA; Board of Regents, the University of Texas  
System  
SO PCT Int. Appl., 57 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000056299	A2	20000928	WO 2000-US6653	20000314
	WO 2000056299	A3	20010118		
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
PRAI	US 1999-125605P	P	19990319		
	US 2000-523886	A1	20000313		
AB	Methods and pharmaceuticals are provided for inhibiting or preventing metastasis formation in animals, including humans, having primary tumors, through the administration of phosphorothioates including their thiol and disulfide metabolites. These compds. stimulate angiostatin levels, inhibit matrix metalloproteinases, and stimulate manganese superoxide dismutase. Phosphorothioates, e.g. amifostine, can be administered as a combination therapy with traditional cancer therapies, including chemotherapy, radiotherapy, surgery, immunotherapy, hormone therapy, and gene therapy. Inhibition or prevention of metastasis by phosphorothioates is independent of tumor type, including adenocarcinomas and sarcomas.				

L8 ANSWER 2 OF 4 MEDLINE  
AN 93268508 MEDLINE  
DN 93268508 PubMed ID: 1338919  
TI [Cancers of the colon and the rectum: news in 1992].  
Cancers du colon et du rectum: nouveautes en 1992.  
AU Rivoire M  
CS Departement de Chirurgie, Centre Leon Berard, Lyon, France.

SO PATHOLOGIE BIOLOGIE, (1992 Dec) 40 (9 Pt 2) 943-8.  
Journal code: 0265365. ISSN: 0369-8114.

CY France

DT News Announcement

LA French

FS Priority Journals

EM 199306

ED Entered STN: 19930702  
Last Updated on STN: 19930702  
Entered Medline: 19930621

AB Five studies presented at the 1992 ASCO meeting are analysed. Kligerman's study was designed to determine if pre-treatment with **WR-2721** could protect normal tissues from the toxicities induced by radiation therapy (in 100 patients with advanced rectal cancer). This pre-treatment resulted in a 13% reduction of moderate and severe acute toxicity. No **WR-2721** patient experienced moderate or severe late toxicities compared to five in the group without pre-treatment. The complete response rate was higher in the **WR-2721** group and there was no major **WR-2721** related toxicity. Minski studied the acute toxicity (during treatment and two weeks after) of combined pelvic radiation therapy, 5-FU and leucovorin when delivered pre-operatively (16 patients) versus post-operatively (25 patients) in patients with rectal cancer. The toxicity criteria were fatigue, diarrhea, tenesmus, bowel movements, dysuria and erythema. Grade 3+ toxicity was more important in the post-operative therapy group (48% versus 13%). Given this high incidence of grade 3+ toxicity future randomized trials should explore the pre-operative approach. The final report of the inter group study of 5-FU plus levamisole as adjuvant therapy for stage C colon cancer was made by Moertel. With a median follow-up time of 5.5 years, the 5-FU plus levamisole treatment has reduced the recurrence rate by 39%, the cancer related death rate by 32% and the overall death rate by 31%. Most of the recurrences occurred during the first two years. There was a **decrease** in the liver, great omentum, peritoneum and **lung metastases**, but there was no modification in loco-regional recurrence rate. (ABSTRACT TRUNCATED AT 250 WORDS)

L8 ANSWER 3 OF 4 SCISEARCH COPYRIGHT 2003 THOMSON ISI

AN 93:210382 SCISEARCH

GA The Genuine Article (R) Number: KU669

TI COLORECTAL-CANCER - WHATS NEW IN 1992

AU RIVOIRE M (Reprint)

CS CTR LEON BERARD, DEPT CHIRURG, 28 RUE LAENNEC, F-69373 LYON, FRANCE (Reprint)

CYA FRANCE

SO PATHOLOGIE BIOLOGIE, (DEC 1992) Vol. 40, No. 9BIS, pp. 943-948.  
ISSN: 0369-8114.

DT Article; Journal

FS LIFE

LA French

REC Reference Count: 3

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Five studies presented at the 1992 ASCO meeting are analysed. Kligerman's study was designed to determine if pre-treatment with **WR-2721** could protect normal tissues from the toxicities induced by radiation therapy (in 100 patients with advanced rectal cancer). This pre-treatment resulted in a 13 % reduction of moderate and severe acute toxicity. No **WR-2721** patient experienced moderate or severe late toxicities compared to five in the group without pre-treatment. The complete response rate was higher in the **WR-2721** group and there was no major **WR-2721** related toxicity. Minski studied the acute toxicity (during treatment and two weeks after) of combined pelvic radiation therapy, 5-FU and leucovorin when delivered pre-operatively (16 patients) versus post-operatively (25

patients) in patients with rectal cancer. The toxicity criteria were fatigue, diarrhea, tenesmus, bowel movements, dysuria and erythema. Grade 3+ toxicity was more important in the post-operative therapy group (48 % versus 13 %). Given this high incidence of grade 3+ toxicity future randomized trials should explore the pre-operative approach. The final report of the inter group study of 5-FU plus levamisole as adjuvant therapy for stage C colon cancer was made by Moertel. With a median follow-up time of 5.5 years, the 5-FU plus levamisole treatment has reduced the recurrence rate by 39 %, the cancer related death rate by 32 % and the overall death rate by 31 %. Most of the recurrences occurred during the first two years. There was a **decrease** in the liver, great omentum, peritoneum and **lung metastases**, but there was no modification in loco-regional recurrence rate. Welt presented a phase I/II study of radio-immunotherapy with I-131-monoclonal antibody A33 in patients with advanced colorectal carcinoma. Results were characterised by major hematologic toxicity and minor tumor response rate. This study (from a leading research team working with one of the best monoclonal antibody) outline the extreme difficulty of cancer therapy with radio-labeled monoclonal antibody. Humanization of A33 is planned to improve these results. Heiss undertook a prospective study to evaluate the influence of homologous blood transfusion on recurrence rate after colorectal cancer surgery. Fifty-eight patients receiving autologous blood transfusion were compared with sixty-two patients receiving homologous transfusion. With a median follow-up of 21 months a higher recurrence rate was found in the homologous group (29.4 % versus 16.7 %). This study methodology is rather criticizable, but its main interest is to focus on the immunosuppressive effect of blood transfusion during surgery in cancer patients.

L8 ANSWER 4 OF 4 MEDLINE DUPLICATE 1  
 AN 83206571 MEDLINE  
 DN 83206571 PubMed ID: 6303574  
 TI Effect of tumor size on S-2-(3-aminopropylamino)ethylphosphorothioic acid and misonidazole alteration of tumor response to cyclophosphamide.  
 AU Milas L; Ito H; Hunter N  
 NC CA-06294 (NCI)  
 SO CANCER RESEARCH, (1983 Jul) 43 (7) 3050-6.  
 Journal code: 2984705R. ISSN: 0008-5472.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 198307  
 ED Entered STN: 19900319  
 Last Updated on STN: 19970203  
 Entered Medline: 19830729  
 AB The influence of tumor size on the ability of S-2-(3-aminopropylamino)ethylphosphorothioic acid (**WR-2721**) or misonidazole (MISO) to alter cyclophosphamide (CY) antitumor activity was investigated, using a chemically induced fibrosarcoma (FSA) and a spontaneous fibrosarcoma (NFSA) in C3Hf/Kam mice. Tumors were of two sizes at the time of treatment, 8-mm leg tumors and 4-day-old micrometastases in the lung. The antitumor activity of CY and its modification were assessed by growth delay of leg tumors and the **reduction** in the number of **lung metastases**. Both measures of tumor response were more pronounced as the dose of CY increased, and FSA was more sensitive to CY than was NFSA. **WR-2721** (400 mg/kg), given 30 min before treatment with CY, reduced the effectiveness of CY on both FSA and NFSA. This reduction in effectiveness of CY was only minimal for leg tumors (dose-modifying factors were 1.1 for FSA and 1.03 for NFSA) but remarkable for lung micrometastases (dose-modifying factors were 1.81 for FSA and 1.55 for NFSA). Protection increased with the increase in the dose of **WR-2721** and was also dependent on the time of injection relative

to CY. The greatest protection occurred when **WR-2721** was given within 30 min before to 15 min after CY. Tumor size had the opposite effect on MISO from that on **WR-2721**. MISO (1 mg/g) enhanced the effect of CY more effectively for leg tumors than for lung micrometastases: dose-modifying factors were 1.74 for FSA and 2.21 for NFSA growing in the leg and 1.27 for FSA and 1.11 for NFSA lung micrometastases. Therefore, tumor size appears to be a very important factor in determining the extent of **WR-2721**- and MISO-induced modification of CY antitumor effect.

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